

**PATENT****Docket No.: HMR2041 US NP1****IN THE UNITED STATES PATENT AND TRADEMARK OFFICE****In re Application of  
Kurt M. Kessler****Examiner: Chang, C.****Serial No.: 09/760,590****Art Unit: 1625****Filed: January 16, 2001****Title: Ethanol Solvate of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8[4R-3S-hydroxy-1-methyl]piperidinyl]-4H-1-benzopyran-4-one**

I hereby certify that this correspondence is being transmitted via facsimile to the Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450, at (703) 872-9306, on

November 10, 2003  
Date of Deposit

Barbara Stein  
Signature

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CENTRAL FAX CENTER****NOV 10 2003****DECLARATION UNDER RULE 132****Commissioner for Patents****Washington, D.C. 20231****Sir:****OFFICIAL**

We, Gary L. Bafus, Christine M. Harrison-Bowman and Gary Lee Silvey each declare that:

1. We are joint inventors of US Patent No. 6,576,647 that was granted from US patent application number 09/760,589, filed on January 16, 2001.
2. We had an obligation to assign the claimed invention of US Patent No. 6,576,647 to a subsidiary of Aventis SA at the time the invention was made.
3. We employed the procedure of Kurt M. Kessler that is disclosed as Example 4 of US Patent No. 6,576,647 to prepare Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate, a crystalline form of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate identified by its characteristic X-ray diffraction pattern.

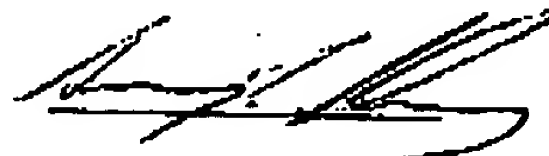
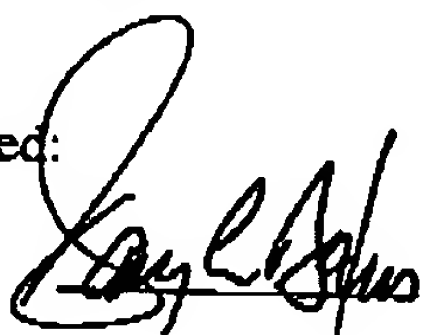
4. We stated and demonstrated in US Patent No. 6,576,647 that said Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate is hygroscopic and that it is an object of the invention to provide a form of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride which features certain superior physical characteristics for use as a pharmaceutical composition.

5. We employed said Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate as starting material for the preparation of the claimed anhydrous or solvate-free Form I of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride that is a crystalline form of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride identified by its characteristic X-ray diffraction pattern. It was further shown that Form I is less hygroscopic at various relative humidities than Form II.

6. As a person signing below, I hereby declare that all statements made herein are of my own knowledge, are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signed:

Date:



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**DECLARATION UNDER RULE 132****Commissioner for Patents****Washington, D.C. 20231****Sir:****I, Kurt M. Kessler, declare that:**

1. I received a M.S. in chemistry from the Philipps Universität Marburg, in 1983 and a Ph.D. in organic chemistry from the Philipps Universität Marburg in 1986. I have been employed as a distinguished scientist at Aventis Pharma Deutschland GmbH and its predecessor companies, Hoechst Marion Roussel and Hoechst AG, from 1986 to 2000. My research activities have been primarily in the field of organic chemistry and medicinal chemistry since about 1983. I am an author of 18 peer-reviewed publications in the areas of organic chemistry and medicinal chemistry, and I am an inventor or co-inventor on 11 patents.

2. I am an employee of Aventis Pharma Deutschland GmbH and I am the sole inventor of the instant patent application, U.S. serial number 09/760,590.

3. I had an obligation to assign the claimed invention of the instant patent application to a subsidiary of Aventis SA at the time the invention was made.

4. I conceived and reduced to practice the procedure disclosed and claimed in the instant patent application for the preparation of Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-

HMR2041 US NP1

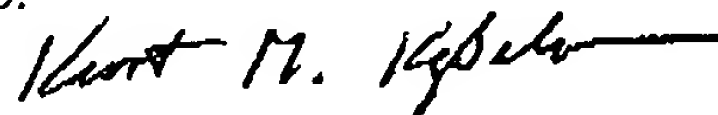
(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate, a crystalline form of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate identified by its characteristic X-ray diffraction pattern.

5. The inventors of US Patent No. 6,567,647 disclosed but did not claim the procedure for the preparation of Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate as is identically disclosed by Example 1 and claimed in the instant application. The inventors of US Patent No. 6,567,647 used the said Form II product as starting material for their claimed invention of anhydrous or solvate-free Form I of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride.

6. I am providing the attached two page Exhibit A in support of my invention and reduction to practice of Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate. The first page of Exhibit A is a copy of signed and witnessed page 53 from my laboratory notebook KK 28, wherein the synthesis of Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate is described below the circled B appearing in the left margin of page 53. The second page of Exhibit A is a copy of NMR H468980 for sample KK 28-53B so obtained, the NMR is referenced at the bottom right of notebook page 53 and the NMR clearly supports the product structure as an ethanol solvate.

7. As a person signing below, I hereby declare that all statements made herein are of my own knowledge, are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signed this 24<sup>th</sup> day of October 2003.



Kurt M. Keßeler